



17/Declaration
1.132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of)
LABERGERIE ERIK ET AL.)
Serial No.09/819,496) Art Unit: 1615
Filed: March 28, 2001) Examiner: R.M. JOYNES

FOR: PULVERULENT MANNITOL AND PROCESS FOR PREPARING IT

ANNEX I

DECLARATION UNDER RULE 132

To Honorable Commissioner of Patents and Trademarks
Washington, D.C.

Sir:

I, Philippe LEFEVRE, of 3600, rue de Merville,
59600 HAVERSKERQUE, France, do solemnly declare:

THAT I am a graduate of "Ecole Nationale de chimie"
- 59000 LILLE - France;

THAT I have been working as chemical engineer since
the 28th of January 1985, and that I now hold the
position of manager of the Pharmaceutical and Cosmetic
Applications Department by ROQUETTE FRERES;

THAT I am well acquainted in the chemistry of
sugars and in particular in the field of pulverulent
mannitol;

THAT I am a named inventor on the present patent
application n° 09/819,496, I am fully familiar therewith
and I am competent to give an opinion regarding the
techniques and subject matter thereof;

THAT I have read and understood the Office Actions
mailed on March 18, 2002 and on January 10, 2003, in
connection with the present patent application;

THAT I have also read and understood US Patent n° 5,573,777 to SERPELLONI et al., in particular the examples of said patent;

THAT I routinely perform measurements of packed bulked density on pulverulent mannitols;

THAT I performed the synthesis of four samples, two according to the invention and two according to SERPELLONI et al., according to the following proceedings:

Sample X 0201 according to the invention:

A vertical SCHUGI FLEXOMIX mixer-granulator is fed continuously via a powder dispenser at a feedrate of 500 kg/hr with a crystalline mannitol manufactured by crystallisation. Such a crystalline mannitol was obtained by crystallization in water (adding of seeds in a saturated solution of mannitol, a standard procedure for a person skilled in the art) and has a particle size determined on a COULTER® LASER LS granulometer of 60 µm.

The mixer-granulator is also fed continuously with a mannitol solution containing 50% by weight of dry matter at 80°C and at a feedrate of 65 l/hr with an atomization nozzle. The rotating knife shaft is previously adjusted to a speed of 3000 rpm.

The moist granulated powder at the outlet of the mixer-granulator falls continuously under gravity unto a SCHUGI fluidised bed dryer-maturer with 4 compartments. In the first 3 compartments the granulated product is dried by air at 120 - 150°C and it then cooled by air at 30°C in the last compartment.

The granulated, dried and cooled product is then sieved continuously on a rotary screen filled with a 740 µm metallic cloth. The pulverulent mannitol



X 0201 thus prepared according to the invention has a mean particle size (laser) of 178 μm .

Sample X 0104 according to the invention:

The manufacture process is identical to the one for the X 0201 sample except that the mixer-granulator is fed continuously with steam at a pressure of 1,3 bar (= 0,13 MPa) and a temperature of 107°C and at a feedrate of 40 kg/hr via an atomization nozzle. The pulverulent mannitol X 0104 thus prepared according to the invention has a particle size (laser) of 126 μm .

Sample E 455 M according to SERPELLONI et al.:

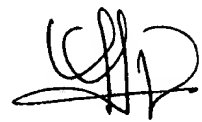
A mannitol solution containing 40% by weight of material maintained is atomized by employing a pilot apparatus marketed by the company NIRO under the name of MINOR MOBILE. The inlet temperature is set at 270°C and the temperature of the feeding mannitol solution is of 120°C.

The atomized powder obtained is then granulated by using a syrup containing 40% by weight of material and then dried by a stream of hot dry air. The thus obtained pulverulent E 455 M thus prepared according to SERPELLONI et al. has a particle size (laser) of 174 μm .

Sample E 272 M according to SERPELLONI et al. :

The manufacture process is identical to the one for the E 455 M sample except that the pulverulent mannitol E 272 M thus prepared according to the invention has a particle size (laser) of 101 μm .

THAT I performed the tests joined in annex on such samples which clearly show that the pulverulent mannitol of the invention differs in its structure and properties from the pulverulent mannitol of SERPELLONI et al. and that this difference allows new applications such as the filling of hard capsules in the pharmaceutical field;



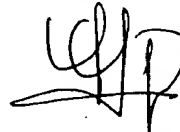
THAT Annex VII shows in particular four test-tubes each one comprising 12 grams of a different sample, the filling of the test-tube (internal diameter: 2,25 cm; external diameter: 2,5 cm; height: 9 cm) having been carried out in the same way, and THAT the height of the powder within the test-tube is different, showing the differences of density of the samples as disclosed below

	Pulverulent mannitol of the invention		Pulverulent mannitol of SERPELLONI et al.	
	LAB 2695 Sample X 0201	LAB 2695 Sample X 0104	PEARLITOL 200 SD Sample E 455M	PEARLITOL 100 SD Sample E 272 M
Packed bulk density	0,72 g/ml	0,71 g/ml	0,54 g/ml	0,58 g/ml
Height of the powder within the test-tube (measured from the tapered basis to the horizontal level)	5,2 cm	5,3 cm	6,7 cm	6,3 cm

I, the undersigned, declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and, further, that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001, of Title 18, of the United States Code, and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 02.04.03

LEFEVRE Philippe



Enclosures: Annex II (table of results), Annexes III to VII (photographs)

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 July 18, 2002

ANNEX II

**TABLE COMPARING THE CHARACTERISTICS OF THE
 PULVERULENT MANNITOL OF THE INVENTION WITH THE
 MANNITOL OF SERPELLONI ET AL.**

	PULVERULENT MANNITOL OF THE INVENTION		PULVERULENT MANNITOL OF SERPELLONI ET AL	
	Lab 2695 Sample X0201	Lab 2695 Sample X0104	PEARLITOL 200 SD Sample E455M	PEARLITOL 100 SD Sample E272 M
Packed bulk density	<u>0.72</u>	<u>0.71</u>	0.54	0.58
Flow factor HOSOKAWA	76	65	81	79
Rate of dissolution in water of the fraction 100 – 200 µm	20 s	20 s	< 10 s	< 10 s
Rate of dissolution in water	40 s	40 s	< 10 s	< 10 s
Average diameter (Laser particle size analysis)	178 µm	126 µm	174 µm	101 µm

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ANNEX III

ELECTRON MICROSCOPE PHOTOS OF THE PULVERULENT MANNITOL OF THE INVENTION - REF LAB 2695 - SAMPLE X0104

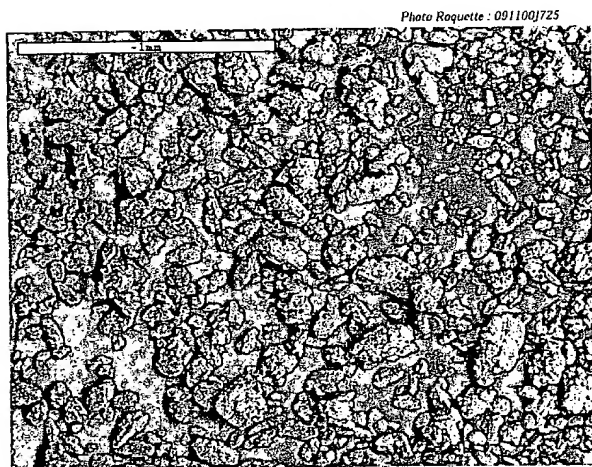


Photo 1: Lab 2695 sample X0104
Magnification: 38.5 X



Photo 2: Lab 2695 sample X0104
Magnification: 154 X

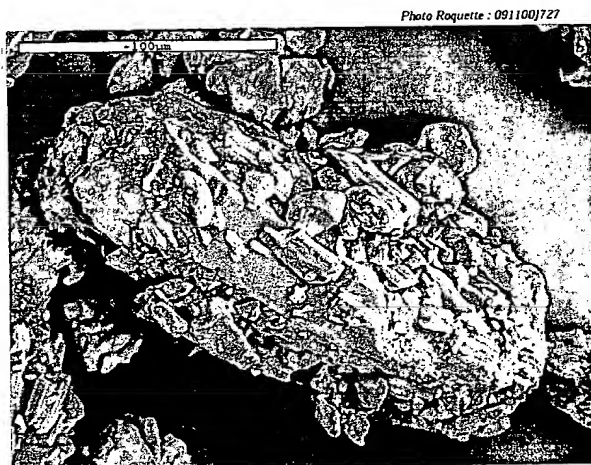


Photo 3: Lab 2695 sample X0104
Magnification: 385 X

ANNEX IV

ELECTRON MICROSCOPE PHOTOS OF THE PULVERULENT MANNITOL OF THE INVENTION - REF LAB 2695 - SAMPLE X201

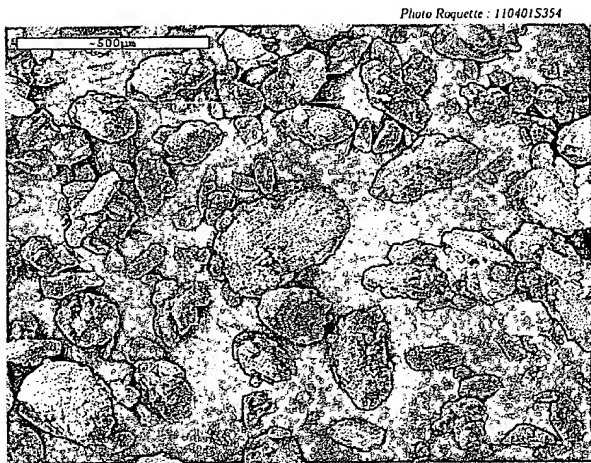


Photo 1: Lab 2695 sample X201
Magnification: 57.5 X

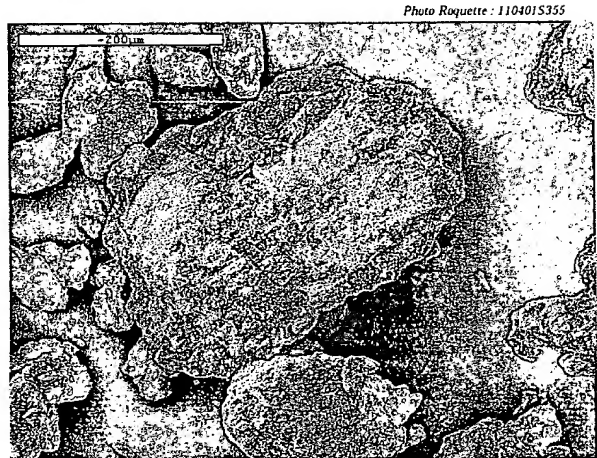


Photo 2: Lab 2695 sample X201
Magnification: 154 X

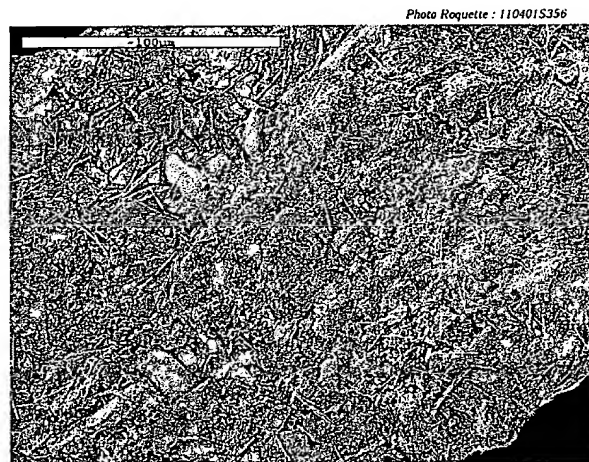


Photo 3: Lab 2695 sample X201
Magnification: 385 X

ANNEX V

ELECTRON MICROSCOPE PHOTOS OF THE PULVERULENT MANNITOL OF SERPELLONI - PEARLITOL ® SD 100 - REF LAB 2515

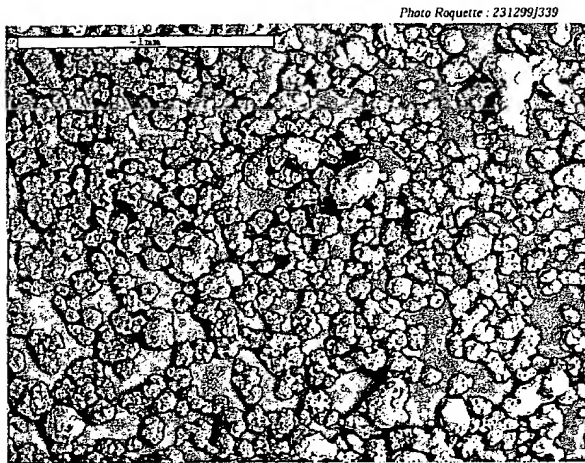


Photo 1: Pearlitol ® SD100 - Lab 2515
Magnification: 38.5 X

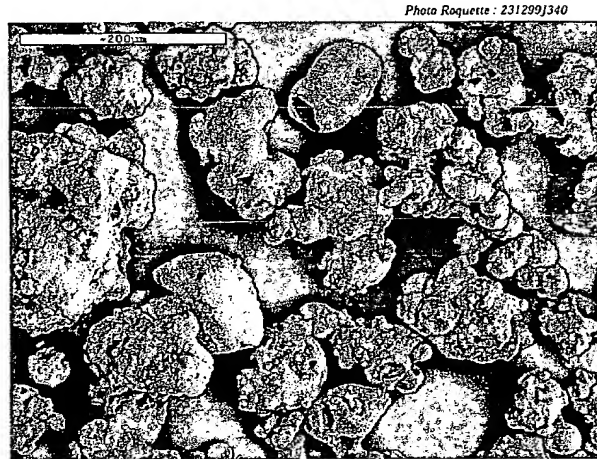


Photo 2: Pearlitol ® SD100 - Lab 2515
Magnification: 154 X



Photo 3: Pearlitol ® SD100 - Lab 2515
Magnification: 385 X

ANNEX VI

ELECTRON MICROSCOPE PHOTOS OF THE PULVERULENT MANNITOL OF SERPELLONI - PEARLITOL ® SD 200 REF LAB E138M

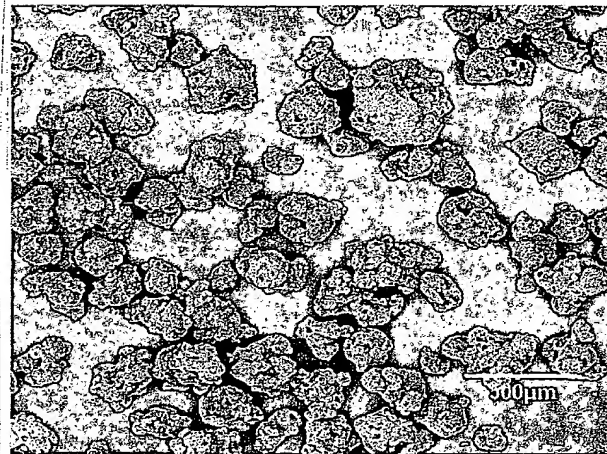


Photo 1: Pearlitol ® SD200 - Sample E138M
Magnification: 35 X

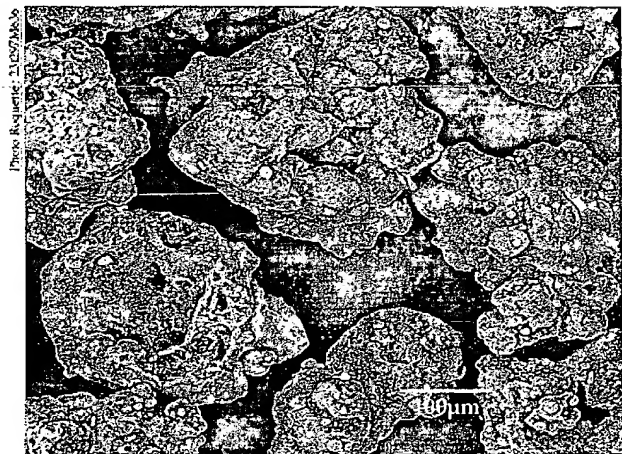


Photo 2: Pearlitol ® SD200 - Sample E138M
Magnification: 146 X

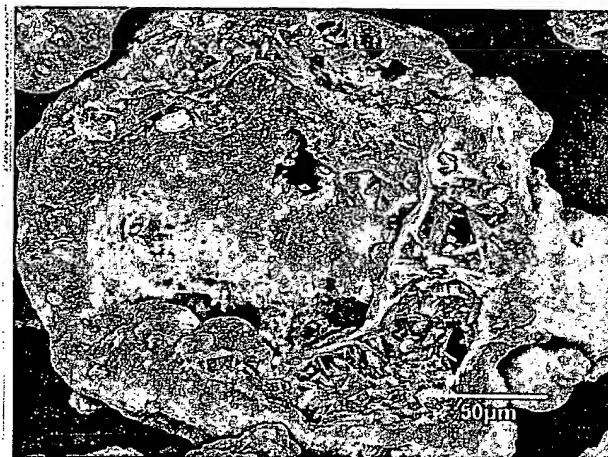
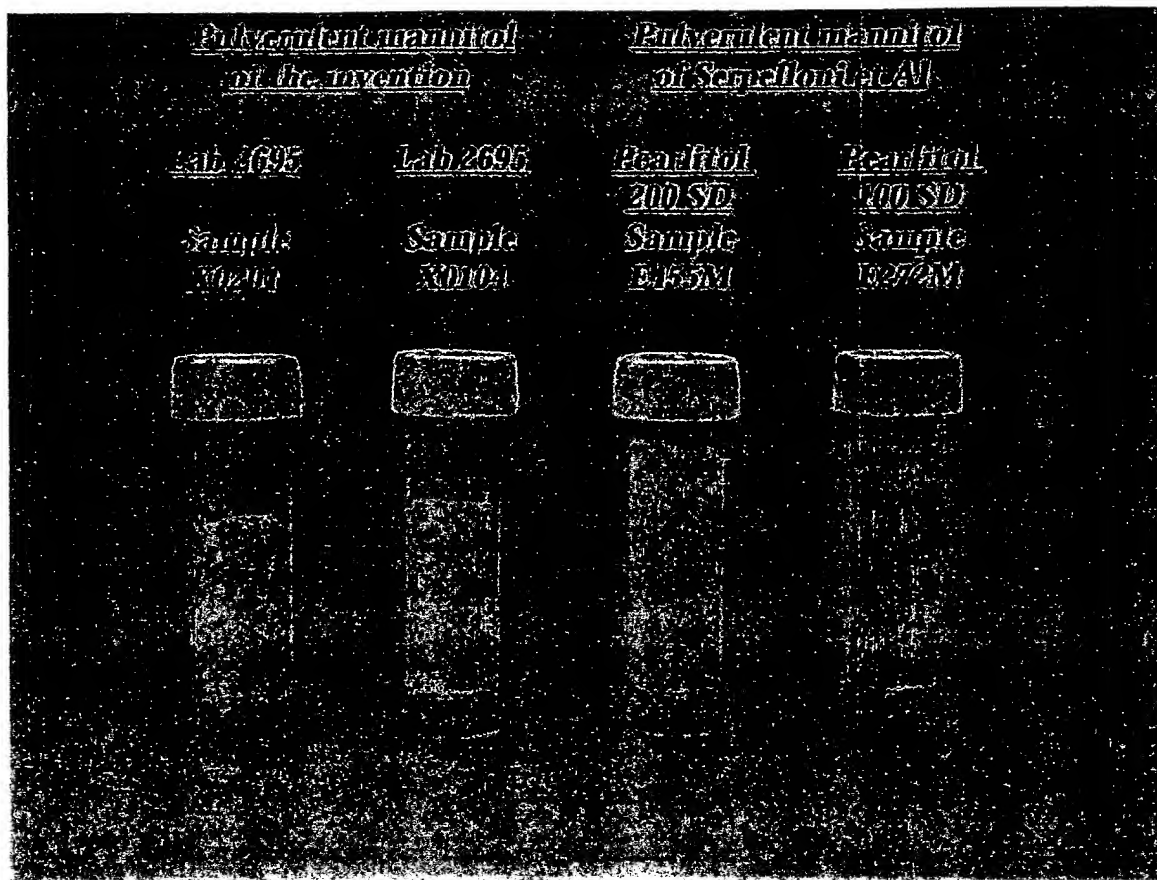


Photo 3: Pearlitol ® SD200 - Sample E138M
Magnification: 365 X



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